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1. mincheff et al. european urology 38 (2) : 208 -217 (2000)

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The Prostate 40:125–129 (1999)

Rapid Communication

Follow-Up Evaluation of a Phase II Prostate Cancer Vaccine Trial

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BACKGROUND. A phase II trial, involving infusions of autologous dendritic cells (DC) and two human histocompatibility antigen (HLA-A2)-specific prostate-specific membrane antigen (PSMA) peptides, was recently completed. Thirty percent of the participants, including subjects with hormone-refractory metastastic disease, and those with suspected local recurrence of prostate cancer, were identified as clinical responders. This report describes the follow-up evaluation of 19 responders in the two study groups.

METHODS. After conclusion of the study, study participants were subjected to follow-up evaluations at 6–8-week intervals. Each responder was reevaluated for response status, and duration of response was determined.

RESULTS. Subjects were observed for an average of 291 days (metastastic group, group A-2) and 557 days (local recurrence group, group B), which included the treatment and follow-up periods. The average duration of response was 149 days for group A-2, and 187 days for group B. A majority of responders (11/19; 58%) were still responsive at the end of the current follow-up.

CONCLUSIONS. The responses observed may be significant and relatively durable. This study suggests that DC-based cancer vaccines in the future may provide an additional therapy for advanced prostate cancer. *Prostate 40:125–129, 1999.* © 1999 Wiley-Liss, Inc.

KEY WORDS: **follow-up evaluation; dendritic cells; prostate-specific membrane antigen; immunotherapy; cancer vaccine; prostate cancer; clinical trial**

INTRODUCTION

Efforts in early detection of prostate cancer, which include serum prostate-specific antigen (PSA) screening and digital rectal examination, allow for diagnoses of the disease at its earliest stages. Treatment strategies such as radical prostatectomy, local radiotherapy, and brachytherapy are largely successful for patients with clinically localized prostate cancer [1,2]. However, up to a third of patients initially diagnosed with clinically localized disease and treated with conventional treatments as mentioned may eventually develop metastases. At this time, the available treatments for metastatic prostate cancer have failed to demonstrate significant curative potential [3].

We recently completed a phase II clinical trial involving patients admitted with presumed local recurrence of prostate cancer after primary treatment failure, as well as those with hormone-refractory metastatic prostate cancer. Each subject received six infusions of autologous dendritic cells (DC) pulsed with HLA-A2-specific prostate-specific membrane an-

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tigen (PSMA) peptides at 6-week intervals. Thirty percent of study participants were identified as responders at the conclusion of the trial [4–6]. This was based on the National Prostate Cancer Project (NPCP) criteria, a 50% reduction in PSA level, or a significant improvement in repeat ProstaScint® scan (Cytogen, Inc., Princeton, NJ) [7,8]. The progress of these responders was monitored beyond the study period to determine the length of response period. This report describes the follow-up evaluation of the responder population at this time.

MATERIALS AND METHODS

Patient Population

The phase II clinical trial reported herein initially enrolled a total of 107 patients. Ninety-five subjects received at least one cycle of infusion, and thus were considered evaluable for response. This population was categorized into group A (subjects with hormone-refractory metastatic prostate cancer, 58 subjects) and group B (subjects admitted with recurrence of prostate cancer after primary treatment, 37 subjects). Group A was further divided into group A-1 (subjects who previously participated in our phase I DC trial, who had requested to enroll in the phase II study), and group A-2 (subjects with no previous immunotherapy trial experience). In this report, we focus on the follow up evaluation of responder populations from study populations with no previous immunotherapy trial experience (i.e., groups A-2 [8 subjects] and B [11 subjects]). All subjects who received hormone therapy prior to the trial remained on the same therapy throughout this trial. If an antiandrogen had been stopped, no patient was entered until at least 3 months had elapsed [9].

Phase II Clinical Trial

Each participant was subjected to leukapheresis at the Fred Hutchinson Cancer Research Center, Seattle, WA (or at Northwest Hospital, Seattle, WA, by alternative blood draws) prior to the start of the trial [5,6]. DC were cultured as described previously [4,5]. Cultured DC were incubated for 2 hr in the presence of 10 μg/ml HLA-A2-specific PSMA peptides (Peninsula Laboratories, Inc., Belmont, CA): PSM-P1(LLHETDSAV) and PSM-P2 (ALFDIESKV). The cells were washed, resuspended in 10 ml injection grade saline, and delivered to the Northwest Hospital Day Surgery/Short Stay Unit. The DC suspension was infused over 30 min with a total volume of 100 ml 0.9% saline. Study participants received a total of six infusions of autologous DC pulsed with a PSM-P1 and -P2 cocktail at 6-week intervals. With each infusion, half the study subjects received a 7-day course of subcutaneous injection of granulocyte-macrophage colony-stimulating factor (GM-CSF, Immunex Corp., Seattle, WA) as systemic adjuvant. At the conclusion of the scheduled infusions and follow-up observations, clinical status was evaluated based on NPCP criteria, a 50% reduction of PSA, or significant improvement in ProstaScint® scan [7,8].

Clinical Monitoring

All participants were subjected to prestudy tests, which included prostate markers, chest X-ray, bone scan, and ProstaScint® scan. Patients were followed during the course of the study with periodic PSA (Tandem-E PSA kit, Hybritech Incorporated, San Diego, CA), free PSA (Tandem-R PSA kit, Hybritech Incorporated), PSMA (in-house Western blot assay), complete blood counts, CHEM-22, and bone alkaline phosphatase (Tandem-R Ostase kit, Hybritech Incorporated) [10]. After the six cycles of infusion were completed, repeat bone scan and ProstaScint® scans were conducted and the results were compared to prestudy results. Prostate biopsy was performed in some patients to confirm ProstaScint® scan results involving the prostatic fossa. After conclusion of the study, subjects were scheduled for periodic follow-up evaluations, which included the tests mentioned previously, at 6–8-week intervals. All testing was conducted on an outpatient basis at Northwest Hospital. Duration of clinical response was calculated from the end of the phase II study for each responder, until disease progression was diagnosed based on NPCP criteria, a 50% increase in PSA value, or a significant progression in ProstaScint® scan.

RESULTS

Phase II Clinical Trial

Six infusions of autologous DC pulsed with two HLA-A2-specific PSMA peptides were administered at 6-week intervals. Table I presents a summary of the two groups, i.e., group A-2 (patients with hormone-refractory prostate cancer) and group B (patients admitted with local recurrence of prostate cancer after primary treatment failure). Thirty-six percent of group A-2 participants died during the trial or follow-up evaluation period. All group B participants were still alive at the end of this observation period. No significant difference in the average number of DC infused was observed between the responder and nonresponder populations of both groups. Group B subjects

TABLE I. Summary of Phase II Clinical Trial Groups*

	Group A-2	Group B
Number of evaluable subjects	25	37
Number of deceased subjects	9	0
Percent decreased	36%	0%
Average (±SEM) DC infused (× 1 million DC)[a]		
Total population	16.6 ± 1.0	18.2 ± 0.7
Responders	17.6 ± 2.4	18.7 ± 0.8
Nonresponders	16.1 ± 1.0	18.0 ± 0.9
Number of responders	8	11
Percent responders	32%	30%
Total period of observation (days)[b]		
Mean ± SEM	291 ± 37	557 ± 19
Median	365	568
Duration of response (days)[b]		
Mean ± SEM	149 ± 24	187 ± 34
Median	144	184

*SEM, standard error of the mean.
[a]Each subject received six infusions of DC/PSMA peptides at 6-week intervals.
[b]The response period was calculated up to January 15, 1999.

received a higher average DC (18.2 ± 0.7 million) compared to group A subjects (16.6 ± 1.0 million).

Comparison of PSA Values Between Responder and Nonresponder Groups

Prestudy PSA values for each study participant were compared to poststudy PSA to determine whether any significant change in these values occurred during the study period. Figure 1 shows significant differences of percent post- vs. prestudy PSA change between responder and nonresponder populations of both group A-2 (P = 0.005) and group B (P = 0.001). Responders in group A-2 exhibited an average 10% decrease in PSA during the trial, while nonresponders showed an average 404% increase. Responders in group B exhibited an average 5% decrease in PSA, while nonresponders showed an average of 100% increase during the course of the trial.

Follow-Up of Phase II Trial Responders

All surviving study participants were requested to participate in long-term follow-up evaluations, which included monitoring of prostate markers, complete blood count, blood chemistry, physical examination, and repeat bone scan and ProstaScint® scan. The average total observation periods were 291 days and 557

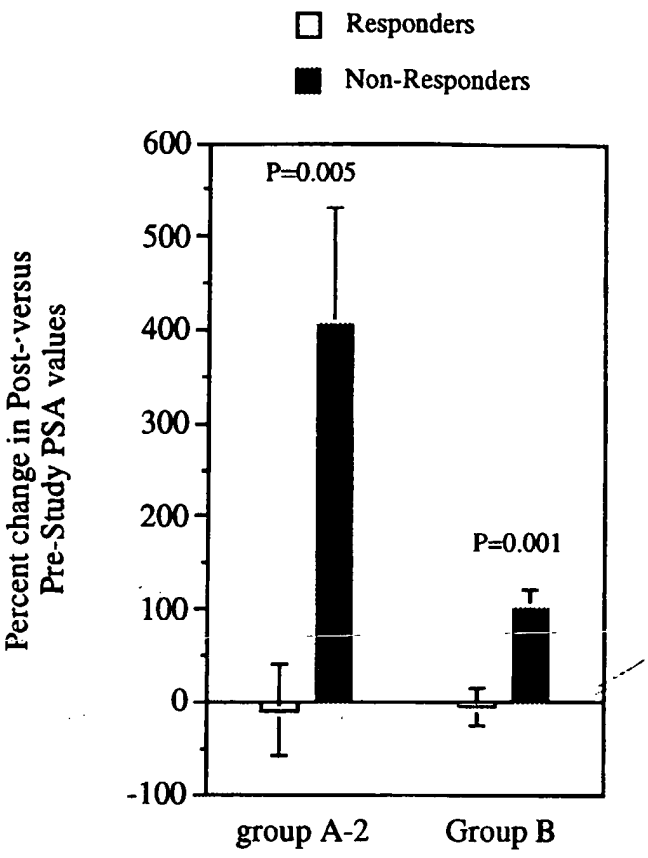

Fig. 1. Comparison of post- vs. prestudy PSA change between responder and nonresponder populations of groups A-2 and B. All study participants were subjected to periodic PSA testing throughout the study period, including prestudy (on the day of infusion 1) and poststudy (3 weeks postinfusion 6). Percent PSA change during the study was calculated as follows: [(Poststudy PSA − Prestudy PSA)/Prestudy PSA] × 100%. The mean and standard error of the mean values are depicted in the bar graph. The values for responder and nonresponder populations were compared using Student's *t*-test. *P* values calculated for groups A-2 and B are shown.

days for participants in groups A-2 and B, respectively (Table I). All responders were reevaluated for their responses using NPCP criteria, a 50% reduction in PSA value, or an improvement in ProstaScint® scan.

The duration of response for each of the responders in groups A-2 and B was calculated from the end of the study to a date where disease progression was determined. The average response period was 149 days for group A-2, and 187 days for group B (Table I). Table II summarizes the response durations of individual responders in both groups. Four partial responders in group A (subjects A, D, E, and H), and four others in group B (subjects 3, 5, 6, and 8) showed a limited response, as their disease progressed between 20–131 days after the end of the clinical trial. The rest of the population, i.e., 4/8 (50%) in group A,

TABLE II. Phase II Clinical Trial Responders From Groups A-2 and B: Duration of Response*

Subject	Stage	HLA-A2	DC infused average[a]	Clinical response	Duration of response (days)[b]
Group A-2					
A	D2	+	13 million	PR	70
B	D2	+	23 million	CR	>156
C	D2	−	12 million	CR	>219
D	D2	−	5 million	PR	131
E	D2	+	24 million	PR	60
F	D2	+	22 million	PR	>175
G	D2	+	20 million	PR	>251
H	D2	−	21 million	PR	126
Group B					
1	D2	+	19 million	PR	>337
2	C	+	20 million	PR	>308
3	D0	+	15 million	PR	20
4	D2	+	20 million	PR	>315
5	D2	+	16 million	PR	105
6	D1	−	22 million	PR	21
7	D0	−	22 million	PR	>185
8	D2	+	19 million	PR	129
9	D2	+	17 million	CR	>211
10	D2	+	16 million	PR	>258
11	D0	+	15 million	PR	>173

*CR, complete response; PR, partial response.
[a]Each subject received six infusions of DC/PSMA peptides at 6-week intervals.
[b]Some patients continued to show a response as of their last evaluation date (up to January 15, 1999).

and 7/11 (63%) in group B, were still responding at the end of the follow-up evaluation period (January 15, 1999). The range of response duration for this group was 173–337 days.

DISCUSSION

Administration of autologous DC pulsed with PSMA peptides to patients with hormone-refractory metastatic prostate cancer, and to those whose primary treatment had failed, was conducted recently at Northwest Hospital (Seattle, WA) [4–6]. Monitoring treatment responses to vaccine therapies has not been an easy task, especially in patients with metastatic prostate cancer who have had a history of hormone therapies and/or dedifferentiated tumors. In addition to the NPCP criteria, periodic measurement of PSA has been an essential tool for monitoring prostate cancer dynamics. Nonresponders in the current clinical trial showed PSA increases of 404% (group A-2), and 100% (group B) during the course of the trial. Furthermore, significant differences in post- vs. prestudy PSA levels ($P < 0.01$) were identified between responder and nonresponder populations in this study (Fig. 1).

However, lack of correlation between PSA levels and the presence of metastases in these patients has also been documented in some cases [11]. Radiodiagnostic imaging (e.g., bone scan and ProstaScint® scintigraphy scan) has provided valuable modalities for identification of measurable bony or soft-tissue metastases months before the appearance of related manifestations or symptoms [8,12]. Within the hormone-refractory metastatic group of the current clinical trial, the majority of subjects (19/25; 76%) had elevated prestudy PSA levels. However, 6/25 (24%) were also admitted with very low levels of PSA. For the latter, decreases in PSA were not a viable criterion for monitoring treatment response. Prestudy tests showed that all of these patients exhibited either a positive bone scan, a positive ProstaScint® scan, or both. Repeat bone and ProstaScint® scan conducted after the conclusion of the scheduled DC infusion were compared to the prestudy results, and were used as additional criterion for response monitoring. Using the combined criteria, 19/62 (30%) were identified as responders from the two groups of the clinical trial.

In order to evaluate whether the responses were durable or not, study participants were afforded periodic follow-up evaluations following the conclusion of the study. Since the majority of responses were identified with repeat ProstaScint® or bone scans, the response duration was calculated starting from the end

of the clinical trial until a disease progression was diagnosed. Four subjects (subjects A and E in group A-2, and subjects 3 and 6 in group B]) had a relatively short response duration (under 100 days). Four subjects responded for over 100 days (subjects D and H in group A-2, and subjects 5 and 8 in group B). A majority of the responders (11/19; 58%), which included 3 subjects who were identified as complete responders and 8 partial responders, had longer response durations ranging from 173–337 days. These latter patients have not shown signs of progression at the end of this period (January 15, 1999). They will continue to be followed and scheduled for periodic monitoring as long as possible. This study suggests that the majority of responses identified in the various groups appear to be durable. DC-based cancer vaccines at some future date may provide additional therapy for advanced prostate cancer.

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